# Exhibit 27

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# *Report on NDMA/NDEA impurities in Valsartan*

of the Plaintiffs' reports, where the main focus is on a hazard-based assessment where dose and exposure are not considered.

## XII. At the Trace Levels of NDMA and NDEA in Valsartan, There Is No Evidence That NDMA/NDEA Causes Cancer in Humans.

I have performed a risk assessment on the low levels of NDMA and NDEA impurities found in valsartan using the BMD approach described above. Risk assessment can be carried out on a compound-by-compound basis. For genotoxic impurities with evidence for a practical threshold, "[t]he existence of mechanisms leading to a dose response that is non-linear or has a practical threshold is increasingly recognized, not only for compounds that interact with non-DNA targets but also for DNA-reactive compounds, whose effects may be modulated by, for example, rapid detoxification before coming into contact with DNA, or by effective repair of induced damage. The regulatory approach to such compounds can be based on the identification of a No-Observed Effect Level (NOEL) and use of uncertainty factors . . . to calculate a permitted daily exposure (PDE) when data are available."[146]

### A. The carcinogenicity potency data for NDMA and NDEA provides sufficient data to calculate a compound-specific Permitted Daily Exposure (PDE).

The liver has shown to be the most sensitive tissue for induction of gene mutations in rats and mice.[147] Therefore, the rat study cancer and mutation data were selected for BMD analysis and PDE calculations enabling comparison of PDEs for cancer and mutation in the same species.[148] We have analysed NDMA and NDEA dose response data to determine

[146] ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (March 2017).
[147] Jiao J, Douglas GR, Gingerich JD, Soper LM, Analysis of tissue-specific lacZ mutations induced by N-nitrosodibenzylamine in transgenic mice, Carcinogenesis 18(11):2239-2245 (1997); Gollapudi BB, Jackson KM, Stott WT, Hepatic lacI and cII mutation in transgenic (lambdaLIZ) rats treated with dimethylnitrosamine, Mutat Res 419(1-3):131-135 (1998); Akagi J, Toyoda T, Cho YM, Mizuta Y, Nohmi T, Nishikawa A, Ogawa K., Validation study of the combined repeated-dose toxicity and genotoxicity assay using gpt delta rats, Cancer Sci 106(5):529-541 (2015).
[148] Gollapudi BB, Jackson KM, Stott WT, Hepatic lacI and cII mutation in transgenic (lambdaLIZ) rats treated with dimethylnitrosamine, Mutat Res 419(1-3):131-135 (1998); Akagi J, Toyoda T, Cho YM, Mizuta Y, Nohmi T, Nishikawa A, Ogawa K., Validation study of the combined repeated-dose toxicity and genotoxicity assay using gpt delta rats, Cancer Sci 106(5):529-541 (2015).

BMDs for each nitrosamine based on existing data and applied various adjustment factors to calculate safe human exposure limits and PDEs. The analysis also provides an opportunity to compare PDE exposure limits derived from in vivo mutagenicity data with those from cancer-studies for both compounds and thereby build on the experience with the use of mutagenicity data for BMD based risk assessments. The values are subsequently evaluated via comparisons with the default TTC for non-nitrosamines as well as for known or estimated human exposures to nitrosamines via foods or therapeutic products (e.g., valsartan).

Using the BMD approach, the PDE were calculated for NDMA and NDEA using gene mutation data and cancer bioassay data. Mutation data were used as proof of concept, to show that there was potential to protect the human population based on exposure limits derived from in vivo gene mutation data. This was successful, and PDE for both NDMA and NDEA were calculated using the 2-year cancer bioassay data in the liver, from male and female rats, following oral exposure, and with an extensive dose range both in the high response and low response regions of cancer incidence.[149] BMD analysis was used to calculate the BMD confidence intervals (BMD CI), and a conservative population size averaging 50kg was used. However, PDE using a larger population size average of 100kg was calculated in **Table 4** and **Figure 13** below, for comparison purposes. Composite uncertainty factors were used, following guidance of ICH 2017[150]: F1, species extrapolation, a default factor of 5 was used; F2, interindividual variability, a maximum value of 10 was used to reflect DNA repair proficiency and metabolism, as a major factor; F3, exposure duration, a factor of 1 was used for the long-term study duration (over 1 year of continuous exposure); F4, severity of effect, since cancer is considered an irreversible effect, a maximum value of 10 was used; F5 was set to 1, as there was no issue with database insufficiency or

[149] Peto et al. 1991a; Peto et al. 1991b.
[150] ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (March 2017).

ability to define a suitable BMDL value, which is considered superior metric than NOEL for use in calculating the PDE.

| | PDEcancer | PDEcancer | PDEcancer | PDEcancer |
|---|---|---|---|---|
| | NDMA | NDMA | NDEA | NDEA |
| BMDL10 (mg/kg) | 0.062 | 0.062 | 0.022 | 0.022 |
| BMDU10 (mg/kg) | 0.107 | 0.214 | 0.046 | 0.092 |
| Human Weight (kg) | 50 | 100 | 50 | 100 |
| Composite UF | 500 | 500 | 500 | 500 |
| PDE (mg/person/day) | 0.0062 | 0.0124 | 0.0022 | 0.0044 |
| PDE(µg/person/day) | 6.2 | 12.4 | 2.2 | 4.4 |
| PDE upper limit (µg/person/day) | 10.7 | 21.4 | 4.6 | 9.2 |

**Table 4:** BMDL10 metrics calculated from liver cancer in Peto et al. (1991)[151] and presented in Johnson et al. (2021).[152] PDEs calculated in line with human weight and uncertainty factor (UF) best practice of ICH, with further justification presented in the recent HESI GTTC publication.[153]

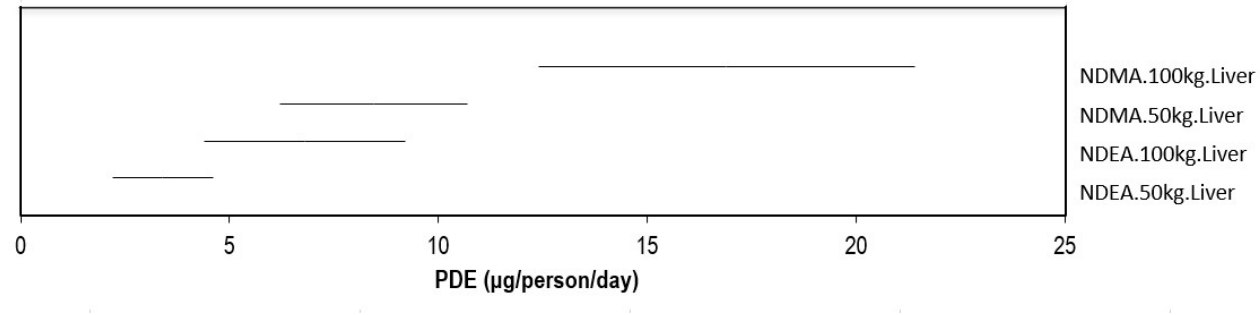


**Figure 11:** PDE confidence intervals (PDE CI), calculated from BMDL10 and BMDU10 for each scenario. PDE were calculated from NDMA and NDEA data in Table 4, and an average population weight of 50kg or 100kg was used.

These PDE for NDMA and NDEA were calculated from the most robust cancer bioassay study. It abided to the OECD guideline, and extended the study to allow for a very precise dose response analysis. There was an oral route of exposure, which has high relevance when calculating the human exposure limits for orally ingested tablets. If the drug and impurity were taken using a nebulizer, an inhaled exposure route may be suitable, or if the drug was

[151] Peto et al. 1991a; Peto et al. 1991b.
[152] Johnson, GE et al., Permitted daily exposure limits for noteworthy N-nitrosamines, Environmental and Molecular Mutagenesis 62:293-305 (2021).
[153] *Id.*

injected, then IP or IV could be relevant; however, those exposure routes are out of scope of the current risk assessment, where the data are excellent and relevant. The range of PDE was calculated and presented in **Figure 11**. This can be used for comparisons to human exposures of NDMA and NDEA. If the NDMA/NDEA exposure dose is within or below the PDE confidence interval, there is no evidence of an increased risk of cancer in humans. I have seen no evidence of cancer being caused in humans at the NDMA/NDEA exposure levels below the PDE. Upon review of the NDMA and NDEA levels published by FDA (Table 1), and applying the calculated PDE range described above and considering the average patient population that would be taking valsartan, it is my opinion that the level of NDMA/NDEA that a patient would reasonably be expected to be exposed to would carry no increased risk of cancer. The level of NDMA/NDEA would be proportionately reduced for the 80mg and 160mg doses of the finished product.

Notably, when the route of administration is oral exposure, the tissues downstream of the liver for metabolically activated substances like these receive much lower levels of the parent compounds and the metabolites, which reduces the amount of DNA damage and tumourigenesis in these downstream organs. Secondary mechanisms, including formaldehyde or reactive oxygen species from NDMA and NDEA, happen at negligible levels and the main risk assessment is therefore around the most potent mechanisms of the CYP-2E1 enzyme, the $O^6$-alkyl-G DNA adduct, the GC>AT mutation with potential for DNA repair by MGMT, multiple mutations in cancer genes and then cancer. The liver is the most sensitive tissue, and the one on which all current risk assessments are based. Where NDMA/NDEA reaches any organ downstream of the liver, if the level of NDMA/NDEA is less than the established PDE, there would be no increased risk of the mutation forming such that it could not be corrected by the DNA repair. I have seen no evidence of cancer being caused in humans where NDMA/NDEA reaches downstream organs at exposure levels below the PDE.

Additionally, NDMA, NDEA and other alkylating N-nitrosamines have been shown to induce similar DNA adduct and mutation spectrum. When DNA is exposed to substances with similar mechanisms of action, the response is through addition. This is a standard risk assessment concept, that was also supported during the FDA 2021 expert workshop in March 2021.[154] Deviation from addition to a synergistic effect, as Plaintiffs' expert propose, is not supported. Therefore, if there were a case to assess two substances such as NDMA and NDEA together, the exposure levels for both substances would be added together, and this would be compared to the AI or PDE of the most potent out of the two substances. This is called dose addition. Any suggestion of a synergistic effect is incorrect.

**B. The "Ten Key Characteristics of Carcinogens" is a hazard analysis and has no application to a risk analysis of a substance with a cancer bioassay.**

The main emphasis of Dr. Panigrahy's analysis is based on 10 key characteristics of carcinogens, which have been developed as a systematic method for evaluating mechanistic data to support conclusions regarding human hazard to carcinogens.[155] The analysis offered by Dr. Panigrahy is a comprehensive analysis of mechanistic data, and can be used to support that NDMA is a carcinogenic hazard – but that was already known and it does not establish or even connect NDMA or NDEA to a cancer risk in humans.

Smith et al. (2016) state that "these developments will aid in advancement of future evaluations of newly introduced agents, ***including those for which mechanistic data provide the primary evidence of carcinogenicity***."[156] For NDMA and NDEA, this is not the case. The Peto et al. 1991 study is arguably the most comprehensive cancer bioassay study to be carried

[154] FDA workshop: Nitrosamines as Impurities in Drugs; Health Risk Assessment and Mitigation Public Workshop (March 29-30, 2021), https://www.fda.gov/drugs/news-events-human-drugs/nitrosamines-impurities-drugs-health-risk-assessment-and-mitigation-public-workshop-03292021.
[155] Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, et al., Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis, Environ Health Perspect124(6):713–721 (2016).
[156] *Id.* (emphasis added).